REMARKS

The Applicant thanks Examiner Wang and Supervisory Examiner Padmanabhan for the courtesy shown during the in-person interview of May 29, 2008 which included Dr. Aldo Iacono, inventor; Ralph Niven, representative of APT Pharmaceuticals, licensee; Andrew Serafini, Esq., patent attorney for licensee; and the undersigned. During the interview, the rejection of claims 19-22, 24, 30, 31, and 49-54 under 35 U.S.C. §103 was discussed.

Claims 19-22, 24, 30-31, and 49-54 are currently pending in this application. Claims 19, 30, 31, and 51-54 have been cancelled, without prejudice; claims 20, 21, 22, and 49 have been amended; and new claims 55-57 have been added. Accordingly, upon entry of this amendment, claims 20-22, 24, 49, 50, and 55-57 will remain pending.

Any cancellation of subject matter by claim cancellation or amendment is made without prejudice to the prosecution of such subject matter in other patent applications.

Rejection of Claims 19-22, 24, 30, 31, and 49-54 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 19-22, 30, 31, and 49-54 under 35 U.S.C. § 103(a) as obvious over Waldrep *et al.* (U.S. Patent No. 5,958,378; "Waldrep"), Hauer *et al.* (U.S. Patent No. 5,342,625; "Hauer"), and Fuji *et al.* (U.S. Patent No. 6,197,829; "Fuji"), in view of Adjei *et al.* (U.S. Patent No. 5,635,161; "Adjei"), Knight *et al.* (U.S. Patent No. 5,049,388; "Knight"), Gordon *et al.* (U.S. Patent No. 6,672,893; "Gordon"), and Iacono *et al.* (*Am. J. Respir. Care Med.*, 1997, 155:1690-1698; "Iacono 1997"), and further in view of Stanford et al. (EP 0372 541; "Stanford").

The Examiner contends that Waldrep, Hauer, and Fuji teach "that cyclosporine is old and well known in combination with various pharmaceutical carriers... particularly, aerosol dosage form." The Examiner also contends that "[t]hese medicaments are taught as useful as immunosuppressant [*sic*] for treating or preventing graft rejections, inflammation and other immunological [*sic*] mediated conditions. . .". The Examiner states that Waldrep, Hauer and Fuji do not teach expressly the various dosage forms, or the dosage levels or the particular time of

administration as claimed in the instant application. However, the Examiner further argues that Adjei teaches that "pulmonary delivery of peptide and protein biotherapeutics, such as cyclosporine, by aerosol is well known in the art," that Knight teaches that "cyclosporine aerosol dosage may be in powder form," and that Gordon discloses that "dry powder is a well known form for pulmonary delivery." The Examiner states that Iacono 1997 "teaches a cyclosporine composition for the treatment of graft rejection." Lastly, the Examiner states that Stanford teaches that immunosuppressive agents are "known to be useful for reducing the frequency of acute transplant rejections."

The Examiner has further rejected claim 24 under 35 U.S.C. § 103(a) as obvious over Waldrep, Hauer, and Fuji, in view of Adjei, Knight, Gordon, and Iacono 1997, and further in view of Armistead *et al.* (U.S. Patent No. 5,665,774; "Armistead"). The Examiner relies upon the reasoning set forth above, and relies on Armistead as teaching that "steroid is useful in treating or prevenling graft rejection."

Applicant respectfully traverses the foregoing rejection. The claims, as amended, are directed to a method for inhibiting chronic graft rejection in a human lung transplant recipient, comprising administering to the transplant recipient, prior to the development of refractory graft rejection, an aerosolized composition comprising an effective dose of cyclosporine, wherein said dose is less systemically toxic than the same dose administered orally, and wherein chronic graft rejection is inhibited in the transplant recipient.

Applicant respectfully submits that, as set forth in *Graham v. J. Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), there are several steps that must be followed in order to properly establish an obviousness rejection under 35 U.S.C. §103. First the scope and content of the prior art are to be determined, then any differences between the prior art and the claims at issue are to be ascertained, and finally the level of ordinary skill in the pertinent art is resolved. It is against this background that the obviousness or nonobviousness of the subject matter is determined by identifying whether one of ordinary skill in the art would have a reasonable expectation of success in achieving the claimed invention by making the proposed combination. (M.P.E.P. §2143; *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Although the Supreme Court has recently asserted that these "Graham Factors" are to be analyzed in a flexible

manner, taking into consideration the common knowledge and common sense of those of ordinary skill in the art, Applicant notes that the Court specifically stated that the above-described factors are consistent with an appropriate test for establishing obviousness. (KSR v. Teleflex, US 550 U.S. __, slip opinion at 15-17 (2007)).

Applicant respectfully submits that the cited art, alone or in combination, fails to teach or suggest, either explicitly or inherently, administering an aerosolized composition of cyclosporine to inhibit ***chronic graft rejection*** in a lung transplant recipient ***prior*** to the development of ***refractory graft rejection***. At most, the cited references suggest the treatment of graft rejection with inhaled cyclosporine only ***after*** development of acute or chronic refractory rejection.

In the Office Action, the Examiner states that one of ordinary skill in the art would have been motivated to "treat the patients of organ transplantation. . . prior to the development of symptoms associated [with] the transplant rejection with the aerosol composition comprising cyclosporine and another immunosuppressant. . . because cyclosporine are [sic] known to be useful for organ transplantation patients. . .and are [sic] particularly known to be delivered through pulmonary delivery." (see page 4 of the instant Office Action). However, contrary to the Examiner's assertions, prior to the instant invention, one of ordinary skill in the art would *not* have been motivated to administer an aerosolized cyclosporine to a lung transplant recipient in accordance with the claimed invention for a number of reasons.

None of the cited references teach or suggest each and every element of the claimed invention. In particular, none of the cited references teach or suggest administering inhaled cyclosporine to a lung transplantation patient *prior to the development of refractory rejection*, to inhibit chronic rejection.

Furthermore, prophylactic treatment of a patient with aerosolized cyclosporine for chronic graft rejection would not have been predicted to provide any additional benefit to the patient prior to the manifestation of development of refractory graft rejection (unresponsive to therapy (*see* Iacono 1997, Abstract, and the instant specification at paragraph [0003])), and would not have been viewed as a reasonable option by one of ordinary skill in the art prior to the invention.

Administration of aerosolized cyclosporine is inconvenient and costly to administer based on the nature of the delivery system and is a potential irritant to the patient (inhaled cyclosporine in propylene glycol can cause coughing, eye irritation, the need for local anesthesia (lidocaine), chest tightness and/or drop in forced expiratory volume in one second (FEV1)) (Iacono et al (2004) *Eur. Resp. J.* 23:384-390 p386 (Appendix A); "only four subjects who began treatments with aerosol cyclosporine were unable to continue with treatment for 2 weeks due to cough, dyspnoea and other symptoms of upper airway irritation"). All of these factors would have contributed to a physician's reluctance to administer aerosolized cyclosporine to a transplant patient prophylactically.

Furthermore, contrary to the Examiner's statement that "a method known for preventing transplantation rejections would reasonably [be] expected to prevent the development of rejections, either chronic or acute" (Office Action dated January 25, 2008, page 5), the disclosure in thc prior art that aerosolized cyclosporine may be used as a treatment for *acute* rejection (vasculitis) does not lead to a reasonable expectation of success that aerosolized cyclosporine will prevent *chronic* rejection (manifested by bronchiolitis obliterans syndrome).

Acute rejection and chronic rejection are pathologically distinct from each other. As stated in Iacono *et al.* ((2006) *N. Engl. J. Med.* 354:141-150, 149) (Appendix B), "[h]istologically, chronic rejection presents in the airways as bronchiolitis obliterans, whereas acute rejection presents as vasculitis." Trulock ((1993) *Chest* 103:1566-1576, at 1570-1574; Appendix C)), also delineates the differences between acute and chronic rejection. As stated in Trulock, "[a]cute rejection is usually readily reversible with treatment and is rarely fatal. In contrast, chronic rejection often responds poorly to therapy and causes considerable late morbidity and mortality." (*Id.* at 1570). Further, as stated in Riise *et al.* ((1997) *Eur. Resp. J.* 10:1742-1746, 1742; Appendix D)), acute and chronic rejection are also diagnosed differently. Riise states that "[c]linically, acute rejection is diagnosed by a combination of histopathological assessment of transbronical biopsies (TBBs) and cytological assessment of bronchoalveolar lavage (BAL) samples." To the contrary, Riise *et al.* states "[c]hronic rejection is diagnosed as therapy-resistant progressive loss of lung function, with the histopathological finding of

obliterative bronchiolotic in lung biopsies. However, [obliterans bronchiolitis] OB is easily overlooked or often not even represented in TBB."

Subsequent studies carried out after the filing of the instant application have shown that aerosolized cyclosporine is not equally effective in the treatment of acute graft rejection and chronic graft rejection. In Iacono et al., ((2006) *N. Engl. J. Med.* 354:141-150, 141; Appendix B), it was shown that "[i]nhaled cyclosporine did not improve the rate of acute rejection, but it did improve survival and extend periods of chronic rejection-free survival."

Based on all of the above, it is clear that acute and chronic rejection are distinct pathological conditions caused by distinct mechanisms, which are not inhibited in the same manner by the same drugs. Therefore, the use of aerosolized cyclosporine for inhibiting acute rejection does *not* lead one of ordinary skill in the art to a reasonable expectation of success for the claimed methods of inhibition of chronic rejection in a human lung transplant recipient prior to the development of refractory graft rejection. Accordingly, the pending claims are not obvious in view of any of the cited art, alone or in combination.

The Examiner further argues, citing *In re Swinehart* (169 USPQ 226 at 229) that "the mere recitation of a newly discovered function or property, inherently possessed by a thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art.

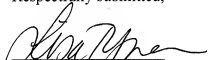
Applicant respectfully assert that the claimed invention was not inherently practiced because in the prior art, aerosolized cyclosporine had not been administered to lung transplant patients prior to the development of refractory graft rejection.

For all of the foregoing reasons, the claims are neither obvious nor inherently anticipated and are patentable over the prior art.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the invention described and defined by the pending claims are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested.

Respectfully submitted,



Lisa B. Kole
Patent Office Reg. No. 35,225

Lisa D. Tyner
Patent Office Reg. No. 51,619

Attorneys for Applicant
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112--4498
(212) 408-2500